Syndrome of the month

The Denys-Drash syndrome

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Drash *et al*[1] described two unrelated children who presented with ambiguous genitalia, both of whom had a unilateral Wilms' tumour, and subsequently developed progressive renal failure. Denys *et al*[2] had previously described a child with male pseudohermaphroditism, Wilms' tumour, and a nephropathy in association with sex chromosomal mosaicism. Review of published reports shows 150 cases[3–64] of what has subsequently been called the Drash or, more correctly, the Denys-Drash syndrome.[65]

Clinical features

GENITALIA

The classical presentation of the Denys-Drash syndrome is in the newborn period as a child with ambiguous genitalia. Although some of the cases of the Denys-Drash syndrome present with normal male external genitalia, the vast majority will appear phenotypically female or have ambiguous genitalia (table 1). The majority of cases of the Denys-Drash syndrome with any one of these three phenotypes of their external genitalia will have a normal male karyotype. The relative paucity of cases with a female karyotype may be because of underdiagnosis of the syndrome in phenotypic females with the nephropathy or as a result of underascertainment because of the previous poor survival of children with renal failure in infancy or early childhood.

The findings in the internal genitalia in the Denys-Drash syndrome are extremely variable (table 2). While the internal genitalia in some of the cases will be appropriate for their external genitalia, it is much more common for the internal genitalia to be inappropriate, that is, Wolffian structures to be present in a phenotypic female, or for both Müllerian and Wolffian structures to be present. In addition, the gonads are often dysgenic (streak gonads or immature, infantile, or rudimentary testicular tissue) or both testicular and ovarian tissue are present or inappropriate for the external genitalia and the chromosomal sex, that is, male pseudohermaphroditism or true hermaphroditism.[66 67]

RENAL FEATURES

The renal involvement in the Denys-Drash syndrome is classically two fold; the development of a progressive nephropathy and Wilms' tumour (table 3). The age of presentation of the nephropathy is usually in the first year. The nephropathy is a primary feature as part of the syndrome and not secondary to other mechanisms as previously suggested, such as

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Table 1 External genitalia findings and chromosomes in the Denys-Drash syndrome

External genitalia	*Chromosomes*	
Male (19/150)	46,XY	7/19
	46,XX	1/19
	BS−	1/19
	ND	10/19
Female (63/150)	46,XY	25/63
	46,XX	15/63
	BS−	1/63
	ND	22/63
Ambiguous (65/150)	46,XY	42/65
	46,XX	0/65
	46,XX/XY	1/65
	BS−	8/65
	BS+	1/65
	ND	13/65
? (3/150)	46,XY	2/3
	ND	1/3

?=not reported, BS +/− buccal smear positive/negative, ND=not done.

Table 2 Internal genitalia findings in the Denys-Drash syndrome

External genitalia	*Internal genitalia*					*Gonads*
	?	*W*	*M*	*W+M*	*N*	
Male	15	—	—	—	—	?
(19/19)	1	—	2	—	—	Dysgenic
	—	—	1	—	—	Ovaries
	—	—	—	—	—	Testes
	—	—	—	—	—	Absent
Female	39	—	—	—	—	?
(65/73)	7	1	8	3	2	Dysgenic*
	2	—	2	—	—	Ovaries
	—	1	—	—	—	Testes
	—	—	—	—	—	Absent
Ambiguous	16	2	2	—	—	?
(62/65)	10	6	8	4	—	Dysgenic*
	—	—	—	—	—	Ovaries
	5	—	2	4	—	Testes
	2	—	—	—	—	Absent

* Dysgenic includes immature, infantile, rudimentary, and dysgenic testes, ovotestis, and fibrous streak.
?=no details, W=Wolffian derived structures, M=Müllerian derived structures, W+M=both, N=neither present.

Table 3 Renal findings in the Denys-Drash syndrome

Nephropathy	143/150 (95%)
Details	104/143
Range of age of onset	0·01–17 years
Average age of onset	1·37 years
Wilms' tumour laterality	111/150 (74%)
Unilateral	89/111 (80%)
Left	15/89
Right	21/89
?	53/89
Bilateral	22/111 (20%)
Age of presentation with tumour	77/111
Range	0·01–13 years
Average	1·65 years

?=not reported.

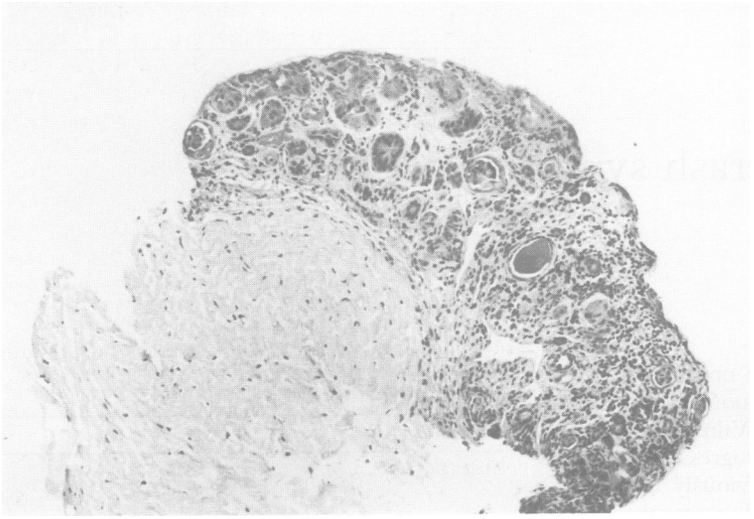

Figure 1 Low power PAS stained slide of a renal biopsy specimen from a child with the Denys-Drash syndrome showing generalised nephrosclerosis with atrophied and dilated collecting tubules.

irradiation to normal kidneys, haemodynamic injury, or hyperfiltration after nephrectomy. If the nephropathy is absent, one might consider the diagnosis of the WAGR syndrome (see below). If, however, the external genitalia are female and the internal genitalia consist of both Müllerian and Wolffian derived structures, or if there are male chromosomes, one can be certain of the diagnosis of the Denys-Drash syndrome.

Renal biopsy typically shows mesangial sclerosis which is classically diffuse but can be focal and is characterised by an expanded fibrillar increase in the mesangial matrix, an increase in the mesangial cells of the glomeruli with hypertrophied vacuolised podocytes, thickened glomerular capillary basement membranes, dilated tubules, often containing hyaline casts, with tubulointerstitial infiltrate and fibrosis[37 48 68] (figs 1 and 2).

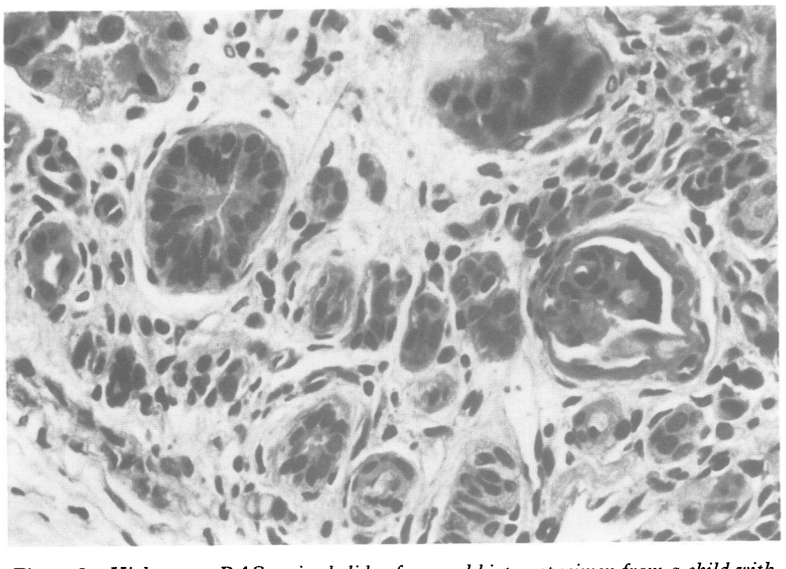

Figure 2 High power PAS stained slide of a renal biopsy specimen from a child with the Denys-Drash syndrome showing a sclerosed glomerulus with a thickened Bowman's capsule and generalised tubular atrophy.

The Wilms' tumour frequently presents as an abdominal mass, but often presents concurrently in a confounding manner with the nephropathy owing to the similar age of onset. It is important to follow up children presenting with apparently isolated Wilms' tumour, especially if there are any abnormalities of the external genitalia, for the possibility of the nephropathy.[42] In the cases with unilateral Wilms' tumour for which information was available, the tumour occurred slightly more frequently on the right.

Not all cases of the Denys-Drash syndrome reported developed a Wilms' tumour. This can be accounted for, in part, by the age of onset of the nephropathy and progression to end stage renal failure in the first year, often before renal dialysis and transplantation was generally available in this age group. The diagnosis of the Denys-Dash syndrome will not be obvious in cases of Wilms' tumour with normal female external genitalia but if the internal genitalia include Wolffian derived structures or dysgenic gonads or both, especially with male chromosomes, one can be certain of the diagnosis of the Denys-Drash syndrome.

GONADAL MALIGNANCIES (TABLE 4)

Six of the children with the Denys-Drash syndrome have developed gonadoblastoma.[29 35 43 51] In four of these the gonadoblastoma was bilateral. In addition, two of the cases with bilateral gonadoblastoma had a unilateral juvenile granulosa cell tumour. The risk for development of gonadal malignancies overlaps with the Frasier syndrome (see below).

Associated findings

There are other physical findings in a number of case reports, some of which are almost certainly incidental (for example, myotonia), others probably being part of the syndrome (for example, structural renal abnormalities) (table 5).

Natural history

For the cases where there is information available, just less than one third were alive at the time of the report, with a range from 3 months to 21 years (table 6). Of those who died, the average age of death was 2 years, with a range from 1 month to just over 7 years. The primary cause of death was renal failure owing to the

Table 4 Gonadal malignancies in the Denys-Drash syndrome

Gonadal malignancies	6/150 (4%)
Type	
Gonadoblastoma	6/8
Bilateral	4/6
Unilateral	2/6
JGCT*	2/8
Unilateral	2/2
Age	
Range	1·25–2·6 years
Average	1·67 years

* JGCT = juvenile granulosa cell tumour.

Table 5 Associated findings in the Denys-Drash syndrome

Type	*No + Ref*
Renal	
Unilateral hyronephrosis	1[12]
Duplication renal pelves/ureters	1[23]
Double left kidney	1[25]
Horseshoe kidney	1[41]
Cardiac	
Ventricular septal defect	1[21]
Miscellaneous isolated	
Inguinal hernia	1[19]
Monozygous twins	1[22]
Contractures	1[45]
Androgen receptor abnormality	1[48]
Sensorineural deafness	1[48]
Congenital nystagmus	1[58]
Multiple	
Cleft palate, mental retardation, nystagmus	1[48]
Aniridia, mental retardation (del 11p13)	1[48]
Cerebral atrophy, mental retardation, chronic bronchitis, low IgG	1[60]
Craniosynostosis, mental retardation, horseshoe kidney	1[60]
Total	15/150 (10%)

nephropathy. It is likely that the prognosis for children with the Denys-Drash syndrome will improve because of increasing availability of renal transplantation.

Management

The management of children with the Denys-Drash syndrome can be likened to "walking a multidimensional tight rope". Monitoring for the progressive nature of the nephropathy is essential. Treatment of renal failure is often determined by the practical difficulties of offering peritoneal dialysis, haemodialysis, or renal transplantation in infancy or early childhood.

Bilateral nephrectomy for children with end stage renal failure owing to the Denys-Drash syndrome has been suggested to obviate the risk of developing Wilms' tumour. More recently it has been suggested that, in children with the syndrome who are hypertensive at the time of instituting dialysis, unilateral nephrectomy should be carried out with the second kidney being removed at the time of transplantation. If the child is not hypertensive, ipsilateral nephrectomy should be carried out at the time of transplantation, screening the remaining kidney with six monthly ultrasound.[69]

Owing to the possible associated risk of gonadal malignancy in some of the cases of the Denys-Drash syndrome, elective gonadectomy should be seriously considered as an option because of the difficulty in effective screening for gonadal malignancies. This is important to keep in mind in the future with the likelihood of improved long term survival as a result of the increasing availability of renal transplantation in the younger child.

Table 6 Natural history of the Denys-Drash syndrome

Alive	48/150 (32%)
Age	
Range	0·25–21 years
Average	4·65 years
Treatment	
Dialysis	8/48
Transplanted	13/48
Death	57/150 (38%)
Age	
Range	0·1–7·5 years
Average	2 years
Cause of death	
Renal failure	46/57
Sepsis	2/57
Wilms' tumour	1/57
Steroids	1/57
Surgery	1/57
Not reported	6/57
Outcome not reported	45/150 (30%)

Differential diagnosis

WAGR SYNDROME

There is phenotypic overlap with Wilms' tumour in association with aniridia, genitourinary abnormalities, and mental retardation (the WAGR syndrome)[70–73] as evidenced by the occurrence of aniridia and mental retardation in one of the cases with the Denys-Drash syndrome.[48] The diagnosis can be difficult in the cases with abnormalities of the external genitalia in association with a Wilms' tumour but without the nephropathy, as previously mentioned.

FRASIER SYNDROME

Frasier *et al*[74] reported a pair of female monozygous twins, one of whom presented with abdominal pain and was subsequently found to have streak gonads with a teratoma, and went on to develop chronic renal failure. Her twin was also found to have streak gonads with a gonadoblastoma in situ. Both twins had a normal male karyotype. Moorthy *et al*[75] suggested that this and subsequent similar reports[58 76–83] represented a separate syndrome, the Frasier syndrome. The nephropathy is similar to that seen in patients with the Denys-Drash syndrome but is usually of a later age of onset.

The reports of occasional gonadal malignancies in a small proportion of the case reports of the Denys-Drash syndrome (see above) suggest that if patients with the Denys-Drash syndrome survive long enough they could be at risk of developing a gonadal malignancy.

NEPHROTIC SYNDROME IN THE FIRST YEAR OF LIFE

In children presenting with nephrotic syndrome in the first year of life, one should consider in the differential diagnosis congenital nephrosis of the Finnish type, idiopathic nephrosis, diffuse mesangial proliferation, minimal change or focal segmental sclerosis, and isolated diffuse mesangial sclerosis.[68 84]

DIFFUSE MESANGIAL SCLEROSIS

Isolated diffuse mesangial sclerosis occurs as a possible autosomal recessive disorder on the basis of a report of five affected persons in an Arab-Israeli family. In addition, it has been reported in a male and female sib pair with associated ocular findings, consisting of nystagmus and absent foveal reflection in the male with mental retardation, while his sister had nystagmus, bilateral optic atrophy, and abnormal maculae.[85]

Aetiology and genetics

The Denys-Drash syndrome usually occurs sporadically. There are, however, reports of one affected male and female sib pair[5] as well as an affected male twin pair.[22]

The demonstration of constitutional deletions of 11p13 as the smallest region of overlap in persons with the WAGR syndrome, and the loss of constitutional heterozygosity of this region, led to the isolation of candidate cDNA sequences and the tumour suppressor gene, WT1, and identification of mutations within it being reponsible for the development of Wilms' tumour.[86–94]

The WT1 gene has 10 exons producing four distinct mRNAs owing to two alternative splice sites in exons 5 and 9 encoding a protein of 45–49 kDa, with features including nuclear localisation, four contiguous Cys_2-His_2 zinc finger domains, and an amino-terminus rich in proline and glutamine, suggestive of its function as a DNA binding protein.[95] The zinc finger domains of the WT1 polypeptide are active during the G_0 to G_1 transition of the cell cycle in cultured cells. The WT1 gene also shows considerable homology to and recognises similar binding sites to the epidermal growth receptor and the Krox family, which are important nuclear intermediates in signal transduction expression.[96]

The WT1 gene is expressed during nephrogenesis in condensed renal mesenchyme, specifically the renal vesicle, and glomerular epithelial cells and would therefore appear to have a role in glomerular development during kidney organogenesis.[97] In addition, high levels of WT1 mRNA expression are observed in developing gonads in early fetal development. In mature gonads, WT1 expression is restricted to the Sertoli cells of testes and granulosa and epithelial cells of ovaries.[91] These findings made the WT1 gene an obvious candidate gene for the Denys-Drash syndrome.

Table 7 Findings in the WT1 gene in the Denys-Drash syndrome

Author	*Mutation*	*Location*	*No*
Pelletier *et al*[51]	C to T missense transition	^{394}Arg to Trp Exon 9—Zn finger III	7
	G to A missense transition	^{396}Asp to Gly Exon 9—Zn finger III	1
	G to A missense transition	^{396}Asp to Asn Exon 9—Zn finger III	1
	G to A missense transition	^{366}Arg to His Exon 8—Zn finger II	1
Bruening *et al*[54]	C to T missense transition	^{394}Arg to Trp Exon 9—Zn finger III	1
	G to A missense transition	+5 of splice donor site within intron 9	1
	G to A missense transition	Cys^{330} to Tyr Exon 7—Zn finger I	1
	G to C transversion	Arg^{394} to Pro Exon 9—Zn finger III	1
Coppes *et al*[55]	C to T missense transition	^{394}Arg to Trp Exon 9—Zn finger III	2
	C to T missense transition	^{377}His to Tyr exon 8—Zn finger II	1
Baird *et al*[57]	C to T missense transition	^{394}Arg to Trp Exon 9—Zn finger III	3
	G to A missense transition	^{395}Asp to Asn Exon 9—Zn finger III	1
	G to A missense transition	^{365}Arg to His Exon 8—Zn finger II	1
	G insertion generates stop codon	Pos 821 Exon 6	1
Poulat *et al*[59]	C to T missense transition	^{394}Arg to Trp Exon 9—Zn finger III	1
Little *et al*[60]	C to T missense transition	^{394}Arg to Trp Exon 9—Zn finger III	1
	G to A transition	^{396}Asp to Asn Exon 9—Zn finger III	1
	T to G missense transversion	^{360}Cys to Gly Exon 8—Zn finger II	1
	C to T transversion	^{362}Arg to Stop Exon 8—Zn finger II	1
	C to G missense transversion	^{373}His to Cys Exon 8—Zn finger II	1
Ogawa *et al*[61]	A insertion Generates stop codon	Position 1534 Exon 9—Zn finger III	
Konig *et al*[62]	G to A missense transition	+5 of splice donor site within intron 9	1
Sakai *et al*[63]	C to T missense transition	^{394}Arg to Trp Exon 9—Zn finger III	2
	G to A missense transition	^{355}Cys to Tyr Exon 8—Zn finger II	1
Clarkson *et al*[64]	G to A missense transition	^{360}Cys to Tyr Exon 8—Zn finger II	1

TYPES OF MUTATION

All of the constitutional mutations so far reported in the Denys-Drash syndrome have been near or within the zinc finger coding region of the WT1 gene[51 54 55 57 59–64 98] (table 7). The same C to T transition missense mutation at amino acid 394 in exon 9 involving the third zinc finger of the WT1 gene has been reported in 17 of the 34 cases of the Denys-Drash syndrome in which a molecular defect has been identified.

The G to A transition at +5 of the splice donor site within intron 9 is the only other mutation reported more than once in the Denys-Drash syndrome.[54 62] This mutation would prevent the production of WT1 isoforms containing exon 9.

A further five have mutations within exon 9 affecting zinc finger III, seven have mutations within exon 8 affecting zinc finger II, and one each have mutations in exons 7 and 6; the former would affect zinc finger I. The latter mutation generates a premature stop codon owing to a frameshift which would result in a gene product without any of the zinc fingers. The adenosine insertion in exon 9 reported would result in an altered reading frame leading to an abnormal proline rich C-terminus of zinc finger III and a truncated gene product missing zinc finger IV owing to generation of a premature stop codon.[61]

Although 22 of the 34 mutations so far identified occur in exon 9 suggesting that mutations in the third zinc finger may be a "hot spot" for mutations leading to the Denys-Drash phenotype,[61] there is no consistent pattern to the mutations reported in the Denys-Drash syndrome. There is, however, marked variation in the phenotypic features seen in the case reports with the most common

mutation, and the same mutation in tumour and constitutional DNA has been reported in a female with isolated Wilms' tumour without any genitourinary abnormalities.[99] In addition, a variety of mutations in the WT1 gene have been reported in patients with isolated Wilms' tumour or with associated genital abnormalities, including deletions of the whole WT1 gene.[91-94]

The means by which mutations in the WT1 gene result in the phenotypic findings seen in the Denys-Drash syndrome could involve the role of the WT1 gene product as a DNA binding protein. Loss of the zinc fingers through generation of premature stop codons or alteration of their function through mutations within the zinc fingers would alter the DNA binding function of the WT1 gene product. It has been suggested that the development of Wilms' tumour occurs through the mechanism of a *trans* dominant gain of function or "dominant negative mutation",[54 60] while it has also been suggested that the renal and genital abnormalities may be the result of a change of function of the WT1 gene product. Alternatively, mutations involving the splice sites would result in alternative splicing of the WT1 gene producing an altered differential expression of the WT1 isoforms.

Suggestions that mutations in the WT1 gene may be responsible for other syndromes or developmental abnormalities have not been borne out by reports to date. Analysis of the WT1 gene in three patients with Frasier syndrome showed no evidence of any mutations in exon 9, although mutations elsewhere in the WT1 gene cannot be excluded.[59] Analysis of the WT1 gene in 12 males with isolated genital abnormalities showed no evidence of mutations although, again, the techniques used for mutational identification cannot exclude the possibility of a mutation being responsible for isolated genital abnormalities.[64]

PARENTS

Analysis of the WT1 gene in 27 parents of 14 cases showed no evidence of the mutation present in their offspring suggesting that in the majority of instances the Denys-Drash syndrome arises as a new mutation.[51 54 55 57 61 63] The father of one case, although phenotypically normal, was shown to be constitutionally heterozygous for the same mutation as his affected child.[55] This latter observation could be either because the father was a somatic mosaic for the mutation, or because of reduced penetrance of the WT1 gene or genomic imprinting. The latter explanation is unlikely as the WT1 gene has been shown to exhibit similar expression with both maternal and paternal transmission.[94]

TUMOUR FINDINGS

Analysis of DNA from the Wilms' tumours from four of the cases showed that they were heterozygous for the same mutation identified constitutionally.[57 60] In three of the patients with the Denys-Drash syndrome,[51] analysis of the tumours showed loss of the normal WT1 allele and the tumours from two of the other cases were homozygous for the constitutional mutation.[60]

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